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Considerations on the use of carrier screening testing in human reproduction: comparison between recommendations from the Italian Society of Human Genetics and other international societies

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Abstract

Purpose Carrier screening (CS) is a term used to describe a genetic test performed on individuals without family history of genetic disorders, to investigate the carrier status for pathogenic variants associated with multiple recessive conditions. The advent of next-generation sequencing enabled simultaneous CS for an increasing number of conditions; however, a consensus on which diseases to include in gene panels and how to best develop the provision of CS is far to be reached. Therefore, the provision of CS is jeopardized and inconsistent and requires solving several important issues.

Methods In 2020, the Italian Society of Human Genetics (SIGU) established a working group composed of clinical and laboratory geneticists from public and private fields to elaborate a document to define indications and best practice of CS provision for couples planning a pregnancy.

Results Hereby, we present the outcome of the Italian working group's activity and compare it with previously published international recommendations (American College of Medical Genetics and Genomics (ACMG), American College of Obstetricians and Gynecologists (ACOG), and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)). We determine a core message on genetic counseling and nine main subject categories to explore, spanning from goals and execution to technical scientific, ethical, and socio-economic topics. Moreover, a level of agreement on the most critical points is discussed using a 5-point agreement scale, demonstrating a high level of consensus among the four societies.

Conclusions This document is intended to provide genetic and healthcare professionals involved in human reproduction with guidance regarding the clinical implementation of CS.

Keywords Carrier screening · Reproductive risk · Reproductive autonomy · Genetic diseases · NGS · Whole-exome sequencing · Cost-effectiveness

Introduction

According to the Clinical Genomic Database of the National Human Genome Research Institute, autosomal and X-linked genetic disorders account for a sizable portion of diseases,

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with approximately 5000 known protein-coding genes specifically connected to recessive disorders [1, 2]. On average, one new disease-gene is discovered every day. Therefore, the aforementioned number of genes causative of recessive disorders is set to increase continuously in years to come [3]. According to the European Organization for Rare Diseases (EURORDIS), 6–8% of the European population is affected by a rare disease, and recessive conditions represent a significant portion of this percentage [4]. Recent data estimate that autosomal (AR) and X-linked (XR) recessive diseases affect 30 out of 10,000 live births. Moreover, recessive disorders explain approximately 20% of infant mortality and up to 10% of pediatric hospitalizations in developed countries [5, 6].

Pathogenic variants for recessive disorders are rarely de novo mutations; instead, they are frequently inherited through multiple generations within the same family. As a result, there are usually many carriers in a family, who are often unaware of their possible carrier status until an affected member of the family is born. In almost all cases, the affected child's parents are phenotypically normal, unaffected heterozygous carriers for one of the causative mutations. The risk of conceiving a child with a recessive genetic disorder is approximately 1–2% for any couple in the general population [7].

Carrier screening (CS) is a genetic test that can be performed on single individuals and couples during their reproductive age, even with a negative family history of genetic conditions. By checking for disease-causing pathogenic variants in the same autosomal genes in both members of the couple (AR diseases) or in a gene on the X chromosome in the female partner (XR diseases), carrier screening seeks to identify couples who are at increased risk of having affected pregnancies [7, 8]. Identification of these at-risk couples (ARC) is the main goal of carrier screening so that genetic counselors can provide them with information on reproductive options to maximize their reproductive autonomy. Preimplantation genetic testing for monogenic disorders (PGT-M), in vitro fertilization with noncarrier donor gametes, and prenatal diagnosis (PND) are some of the reproductive alternatives that can be prospected to couples during genetic counseling after positive carrier screening results.

Carrier screening for inheritable AR conditions began in the 1970s, with the screening of at-risk populations distinguished by geographical isolation and customs that limited random mating (ancestry-based screening).

The first population to be screened for a recessive disorder was the Ashkenazi Jewish (AJ) for Tay-Sachs disease (TSD). TSD is a severe AR condition with a carrier frequency of 1/30 in the AJ population and 1/300 in the general population [9]. This first recorded CS program provided the necessary proof of principle for subsequent screening initiatives, including population-specific programs such as those for thalassemia (OMIM #613,985) in individuals from Mediterranean regions or the one for cystic fibrosis (CF, OMIM #219,700) in populations of European ancestry [10, 11]. However, restricting carrier screening by using socially defined ethnic constructs or by self-identified ancestry is both inequitable and scientifically flawed [12, 13]. Nowadays, the most widely accepted form of CS is the so-called pan-ethnic or universal. This screening approach aims to identify carriers of genetic diseases with high frequency in the general population.

Over the last 50 years, technological advances have drastically changed the molecular testing of pathogenic variants. Particularly, the availability of the next-generation sequencing (NGS) has made possible the inclusion of an extensive number of disorders, up to whole-exome and whole-genome approaches, in a reliable, high-throughput, and cost-effective way. Moreover, the generation of databases for the classification of genomic variants and the outstanding rate of discovery of new disease-causing genes have broadened the diagnostic yield, particularly for rare recessive disorders [14, 15]. Taken together, these improvements make it possible for prospective parents to participate in CS programs assessing simultaneously the genetic risk for tens to hundreds of recessive diseases, regardless of the family history and the ethnic background. Contemporary CS programs can get a diagnostic yield as high as 2–5% of couples tested that are shown to be at increased risks following genetic screening [7, 16–18].

Scientific societies, including ACOG (American College of Obstetricians and Gynecologists), recognize that the extension of preconception genetic screening tests for the most common and severe recessive conditions to healthy individuals without family history is an acceptable strategy and crucially beneficial, provided that proportionality criteria of the testing strategy are met [19, 20].

However, CS is not yet routinely offered for preconception/pregnancy risk assessment probably due to inconsistency with good practice recommendations in its early application (particularly for the gene panel to screen) and poor development of national scientific and educational programs for the provision of CS to the broader community.

Indeed, CS application resulted in a wide heterogeneity of commercially available panels for CS testing. For example, in 2018 a report of data from 16 laboratories showed that the number of conditions screened by different commercial panels ranges from 41 to 1792 [21]. However, only three conditions are shared by all reviewed CS panels (cystic fibrosis, Niemann-Pick, and Maple syrup urine diseases) alongside broad differences in both the interpretation criteria and the applied laboratory techniques. Furthermore, very few national/regional scientific societies have developed specific guidelines for the implementation and adoption of CS in their territories.

Due to the high ethical and clinical impact of CS screening, scientific organizations recently felt the need to publish updated guidelines for CS use, including benefits/limitations and technical and ethical foundations to consider for the design and development of CS programs [22–26]. The purpose of this work is to cover recommendations recently developed in Italy by the Italian Society of Human Genetics [27] as well as those proposed at the international level, commenting on the key elements of novelty as well as their main agreements and differences.

Methodology: recommendations in Italy and worldwide

Initially, the Italian Society of Human Genetics (SIGU) recommended not to perform genetic tests for the risk assessment of monogenic diseases in both scenarios of natural conception and medically assisted reproduction (MAR) [28, 29]. In 2016 this statement was revised, and screening for CF was recommended because of its correlation to male infertility [30, 31]. Likewise, the American College of Medical Genetics and Genomics (ACMG) [23] and the American College of Obstetricians and Gynecologists (ACOG) [25] recommended generalized (pan-ethnic) screening only for CF and spinal muscular atrophy (SMA, OMIM #253,300).

However, future clinical use of CS tests during the preconception stage was not rejected, if supported by analytical and clinical evidence. Acknowledging the advances in the technology used in carrier screening, the criteria have changed over time.

In 2020 SIGU has set up a working group composed of geneticists with hands-on expertise in different branches (cytogenetics and cytogenomics, clinical genetics, molecular genetics, forensic genetics, pharmacogenetics, epigenetics, and healthcare providers) to discuss the provision of CS. The working group members defined an outline for relevant and challenging topics and later discussed them in depth with the entire group until consensus. Several online meetings were organized for discussion, and finally, the draft of the proposed document was submitted for stakeholder review. The final version was approved on 20 July 2021 and published on the SIGU website on 4 October 2021 [27].

The following scientific societies, whose most recent official documents regarding carrier screening were released between 2017 and 2021, might be considered as representative international guidelines: ACOG, which upholds the earlier version [8, 25], the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) [24], and ACMG [22].

By comparing the cited above documents to one another and to the final statements of the Italian working group, we have determined a consensus-based core message on genetic counseling and nine main subject categories to explore, spanning from goals and execution, to technical scientific, ethical, and socio-economic issues.

The following text will go over each of the nine subjects in detail, along with the genetic counseling component, focusing on SIGU recommendations and providing a condensed summary of the statements from the other three societies at the end of each paragraph.

To facilitate the comparison among societies, the main recommendations of the four organizations are summarized in Table 1.

1. Carrier screening goals

The use of CS should meet the requirements of the ACCE framework, which developed the first publicly available analytical process for evaluating scientific data on emerging genetic tests that has been adopted by various entities worldwide [32, 33]. ACCE considers four main criteria for the evaluation of a genetic test (i.e., analytic validity, clinical validity, clinical utility and associated ethical utility, legal and social implications, ELSI). Analytical validity (e.g., sensitivity, specificity) refers to a test's capability to detect the genotype of interest accurately and reliably. Clinical validity (e.g., positive/negative predictive values) refers to a test's ability to predict the clinical disorder or phenotype associated with the genotype. Clinical utility of a test results in changes in clinical endpoints, conditioned on test results. ELSI includes all non-technical issues that arise when developing emerging science and technologies and implementing them in society, as described in the corresponding section below.

First, analytical validity of carrier screening is to be established by genetic laboratory through robust validation processes as requested by supervisory authorities. Clinical validity and utility for carrier screening are defined by the detection of couples at increased risk of transmitting a genetic disorder to their offspring (i.e., diagnostic yield of a specific EC assay) and the possibility to provide them with several reproductive options, respectively.

SIGU reports as the primary objective of carrier screening, to facilitate reproductive autonomy and support informed decision-making rather than to demonstrate the possible reduction of affected children's births [23, 25, 34]. Regarding carrier screening goals, ACOG provides individuals with meaningful information to guide pregnancy planning based on their personal values, in agreement with SIGU. More directly, RANZCOG and ACMG emphasize the identification of couples at risk who have a 1 in 4 chances of each pregnancy to have conceive a child affected by a recessive genetic disorder.

Table 1 Comparison of CS recommendations from the four organizations considered with 5-point agreement scale (1 or strongly agree, consensus endorsement; 2 or agree, endorsement with a minor point of contention; 3 or mixing, nuanced statements; 4 or disagree, split in two opposite perspectives; 5 or strongly disagree, divergent positions). Abbreviations: *WES* whole-exome sequencing, *MLPA* multiplex ligation-dependent probe amplification, *PCR* polymerase chain reaction, *rt* real-time PCR, *q* quantitative-PCR, *AR* autosomal recessive, *XR* X-linked recessive, *CF* cystic fibrosis, *SMA* spinal muscular atrophy, *FXS* Fragile X syndrome, *AJ* Ashkenazi Jewish, *TSD* Tay-Sachs disease, *CS* carrier screening, *IC* informed consent. Symbols: * as novelty element of SIGU recommendations

	SIGU (2021–2022, [25])	ACMG (2021, ref.[20])	ACOG (2017, ref. [8, 20])	RANZCOG (2019, ref. [22])	Grade of agreement
Carrier screening goals	Facilitate reproductive autonomy and informed decision-making	Define the reproductive risk for the couples and identify those at risk for transmitting genetic diseases to their offspring	Facilitate reproductive autonomy and informed decision-making	Define the reproductive risk for couples and identify those at risk for transmitting genetic diseases to their offspring	Agree-based recommendation
Recipients	- Individuals/couples planning pregnancy or who are pregnant	-Individuals/couples planning pregnancy or who are pregnant	-Individuals/couples planning pregnancy or who are pregnant	- Individuals/couples planning pregnancy or who are pregnant	Strongly agree-based recommendation
	- Consanguineous couples	- Consanguineous couples	- Consanguineous couples	- Presence of consanguinity and/or family history	
	- Gamete donors*				
Timing and how to perform the test	- Pre-conceptional stage should be preferred	- Pre-conceptional stage should be preferred	- Pre-conceptional stage should be preferred	- Pre-conceptional stage should be preferred	Strongly agree-based recommendation
	- Contextual or sequential approach	- Contextual or sequential approach		- Contextual or sequential approach	
	-Contextual approach should be used during the pregnancy	-Contextual approach should be used during the pregnancy			
Methods of analysis	- Next-generation sequencing via targeted sequencing of selected genes or via WES	-Next-generation sequencing	Next-generation sequencing	Next-generation sequencing	Agree-based recommendation
	- Ancillary molecular testing: MLPA, qPCR, rtPCR	- Other methods: PCR, MLPA, Sanger sequencing, microarray			

Table 1 (continued)

	SIGU (2021–2022, [25])	ACMG (2021, ref.[20])	ACOG (2017, ref. [8, 20])	RANZCOG (2019, ref. [22])	Grade of agreement
Which and how many conditions?		- Carrier frequency of 1 in 200 or greater	- Carrier frequency of 1 in 100 or greater		Mixing-based recommendation
	- Well-defined genotype–phenotype correlation	- Well-defined genotype–phenotype correlation	- Well-defined phenotype		
	- Unfavorable effect on the quality/duration of life	- Phenotype severity	- Unfavorable effect on quality of life	- Unfavorable effect on the quality/duration of life	
	- Physical and/or cognitive impairment		- Physical and/or cognitive impairment		
	- Requirement of medical and/or surgical intervention		- Requirement of medical and/or surgical intervention		
	- Early onset		- Early onset		
	- Available appropriate diagnostic procedures. options	- Available prenatal diagnosis and reproductive options	- Available prenatal diagnosis and opportunities for intervention		
		- Established analytic validity of screening methods			
	→ No list of disease to analyze on all couples	→ Tier 3 for AR and XR diseases listed on all couples	→ Exclusively CF on all couples	→ Thalassemia, CF, SMA, and FXS on all couples	
				→ On AJ descent: TSD, Niemann Pick disease type A, Fanconi anemia group C, familial dysautonomia, Bloom syndrome, Canavan disease, and mucolipidosis type IV	
Reporting of the result	- Class 4 and 5 variants only should be reported, while those of class 3 should not	- Class 4 and 5 variants should be reported	- No recommendation about which variants should be reported	- Class 4 and 5 variants only should be reported, while those of class 3 should not	Strongly agree-based recommendation
		- Class 3 variants can be considered in specific circumstances			
	- Residual risk should be provided	- Whenever possible, residual risk should be provided	- Whenever possible, residual risk should be provided	- Presence of residual risk	
	Annexed report templates				
Cost-efficiency evaluation	- Not enough data and further studies needed	- Not enough data and further studies needed	- Not enough data and further studies needed	- Not enough data and further studies needed	Strongly agree-based recommendation
Ethical reflections	Justice, autonomy, and consequences evaluation	Equity and inclusion	None	Equity and inclusion	Agree-based recommendation

Table 1 (continued)

	SIGU (2021–2022, [25])	ACMG (2021, ref.[20])	ACOG (2017, ref. [8, 20])	RANZCOG (2019, ref. [22])	Grade of agreement
Informed consent	- CS is voluntary, and results are confidential	- CS is voluntary, and results are confidential	- CS is voluntary and results are confidential		Mixing-based recommendation
		- Conditions of varying severity are included	- Conditions of varying severity are included		
		- Reproductive risk assessment depends on accurate knowledge of paternity	- Reproductive risk assessment depends on accurate knowledge of paternity	- When a reproductive partner has changed, carrier screening should be readdressed	
	- A negative screen does not eliminate risk to offspring	- A negative screen does not eliminate risk to offspring	- A negative screen does not eliminate risk to offspring	- A negative screen does not eliminate risk to offspring	
		- Being a carrier of an AR condition has no clinical consequences for the individual carrier. If each partner is identified as a carrier of a different AR condition, offspring are not likely to be affected	- Being a carrier of an AR condition has no clinical consequences for the individual carrier. If each partner is identified as a carrier of a different AR condition, offspring are not likely to be affected		
		- There is a small chance of identifying the individual tested as affected by one of the conditions screened for	- There is a small chance of identifying the individual tested as affected by one of the conditions screened for	- There is a small chance of identifying the individual tested as affected by one of the conditions screened for	
	Annexed IC template and information notice				

2. Recipients

Recipients of the test are couples of reproductive ages who are planning a pregnancy, either naturally or through medically assisted reproduction (MAR), regardless of positive family history or ethnic background. Thus, SIGU endorses to widen the use of CS from previous cases with known family history or based on ancestry to healthy individuals without family history. Regarding this topic, the other scientific societies substantially agree that screening should be offered to all couples, as it is an acceptable strategy and crucially beneficial. Furthermore, the SIGU working group remarks that CS should be particularly encouraged to consanguineous couples, because of the higher probability to conceive a child affected by recessive diseases.

The SIGU working group outlined that CS plays a pivotal role in gamete donation programs in the context of MAR. Particularly, given the fact that a single donor may be involved in a greater number of conceptions than with homologous MAR cycles. Therefore, if the donor is a carrier of a recessive condition, this will be associated with an increased risk of having an affected offspring at every conception. In case of female donors, a further care should be taken with X-linked recessive diseases, possibly enriching CS panels for these conditions.

3. Timing and how to perform the test

Regarding the timing, the SIGU working group outlined that pre-conceptional stage should be preferred. When performed on couples who are planning a pregnancy, the test allows for early reproductive risk identification, giving patients a broader range of reproductive options, ranging from preimplantation genetic testing to prenatal diagnosis [7].

The SIGU working group considered that CS can also be performed in early gestational weeks (no later than the 12th), to inform about reproductive risks in a period which is compatible with a prenatal invasive diagnostic procedure, such as chorionic villus sampling (CVS) or amniocentesis. However, CS should not be encouraged in the prenatal period, due to time-sensitive constraints related to clinical results interpretation and the need for a possible invasive prenatal diagnosis. The SIGU working group recognized and acknowledged the lack of proper frameworks in the country to deliver timely and appropriate education and knowledge to facilitate informed decision-making at the preconception stage. Therefore, future efforts should be invested in the development of strategies that are able to promote and bring education and awareness about CS to the general public in a timely fashion.

Referring to how the test should be performed, the SIGU working group supported a contextual CS approach (both partners' samples are collected and tested simultaneously) or, whenever not possible, a sequential one (the addition of sampling and testing of the second partner, generally the man, if the first one, generally the woman, is positive). Importantly, if the screening test is carried out during the pregnancy, the contextual approach must be used, providing a faster turn-around-time with a comprehensive information.

Regarding this third point "Timing and how to perform the test," all societies agree that the ideal time for carrier screening is prior to conception and discussion of the different approach (i.e., contextual/couple testing or sequential/one-member screening strategy). In particular, SIGU and ACMG recommend that if CS test is done in pregnancy, it should be offered to both partners at the same time (Table 1).

4a. Method of analysis: NGS–WES and target sequencing

Recently, CS techniques have been developed based on NGS to screen simultaneously many genes associated with AR or XR genetic disorder. The main approach is analyzing the protein-coding regions of these genes since most of the known disease-causing variants (> 85%) are located there [35]. When using NGS analysis, SIGU recommends performing a preclinical validation to ensure the highest levels of accuracy in sequencing and variant calling performance. Moreover, the quality criteria (QC) should be assessed during each analytical session. The qualitative parameters per variant should be coverage ≥ 30×, heterozygosity of > 35%, and base call quality score of ≥ 20. Overall, if these requirements are met, the SIGU working group considers the unnecessary confirmation of positive variants identified by NGS by orthogonal molecular techniques [36–39].

In terms of clinical validity, a sufficiently high detection rate is required in order to significantly reduce the residual risk. The detection rate for each gene/condition included in CS analysis should not be lower than 85% if only one member of the couple is screened or less than 70% if both members of the couple are screened.

Different analytical NGS strategies can be performed: (i) customized panel which includes the sequencing and analysis of selected genes and (ii) whole-exome sequencing (WES) followed by filtering of genes of interest. Panels usually offer better coverage and analytical reproducibility than WES for the same subset of genes, even though analytical performance are constantly evolving and improving for WES.

Nowadays, SIGU supports the use of NGS and considers that SNP array-based approaches as CS techniques are obsolete and inappropriate, due to their limited analytical and clinical validity (e.g., low coverage for each gene) [40].

Documents from other scientific societies did not take particular consideration on the technology to use: ACMG lists all the methods to identify genetic changes including

single-nucleotide variants (SNVs) and copy-number variants (CNVs), as reported by SIGU; more generally, ACOG and RANZCOG mention the advent of NGS.

4b. NGS limitations and use of ancillary molecular testing

Despite its technical reliability, some complex genomic regions (e.g., pseudogenes, large structural genomic rearrangements, CNVs, triplet expansions, non-coding regions) cannot be investigated with NGS-based approaches and require specific ancillary tests.

As an exemplary case, recent studies suggest that CNVs could represent a not negligible portion of the pathogenic variants in some genes, such as *DMD*. In this regard, techniques such as multiplex ligation-dependent probe amplification (MLPA) must be employed. Thus, SIGU suggests to always perform these ancillary molecular tests to improve the diagnostic yield of CS for some specific conditions (e.g., FRAXA and SMA), with a high prevalence of carriers, whose mutations are not single-nucleotide variants (e.g., CGG repetitions in the *FMR1* gene and exon 7 deletions in *SMN1* gene) [16, 41].

5. Which and how many conditions?

To avoid an indiscriminate increase of the analyzed conditions, the SIGU criteria for the inclusion of a gene in the panel should be the following ones, provided that analytical and clinical validity of the CS testing are met:

1. The condition must be associated with a well-defined phenotype (with a well-documented genotype–phenotype correlation).
2. The condition must result in an unfavorable effect on the quality/duration of life.
3. The condition must be causative of physical and/or cognitive impairment.
4. The condition must require medical and/or surgical intervention.
5. The condition must present with an early onset (meaning that late-onset conditions should not be included in the panel).
6. Appropriate diagnostic procedure or preimplantation genetic testing must be available.

Overall, SIGU does not provide a list of diseases to analyze, as this can easily change over time as new knowledge arises.

It should be reminded that, among the 1300 autosomal recessive and X-linked conditions currently identified, about a hundred of them show a disease prevalence equal or higher than 1/100,000 corresponding to a carrier frequency of 1/158 [42].

Even if the carrier frequency should be considered, a defined cut-off frequency does not appear among the SIGU inclusion criteria. This is because the scientific evidence used to establish carrier frequency can vary and generate a not precise and uniform estimation. Moreover, despite being widely used, a carrier frequency higher than or equal to 1/100 limits the diagnostic yield: carrier frequency can vary between ethnic groups, and as a result, the cut-off 1/100 becomes too strict if applied in pan-ethnic approaches [35].

Regarding the topic of "Which and how many conditions," these are the main differences among scientific societies:

- ACOG gives several guidelines about which conditions should be screened for (have a carrier frequency of 1 in 100 or greater corresponding to a disease frequency of 1/40,000; have a well-defined phenotype; have a detrimental effect on quality of life; cause cognitive or physical impairment; require surgical or medical intervention; have an onset early in life; can be diagnosed prenatally; and can provide possibility of an ante-perinatal intervention and/or a better postnatal management to improve newborn and infant outcomes). ACOG recommends the pan-ethnic screening exclusively for CF.
- Generically, RANZCOG claims that the selected conditions should be a cause of major diminution of quality of life and/or reduction in lifespan. Screening for thalassemia, CF, SMA, and FXS should always be offer to the general population. Moreover, RANZCOG mentions additional conditions that should be screened in some specific populations, such as AJ ancestry.
- Historically, ACMG gives inclusion criteria for CS design (phenotype severity, high prevalence of carriers in the screened population, established analytic validity of screening methods, predictable genotype–phenotype correlation, available prenatal diagnosis and reproductive options). Based on that, ACMG recommended the screening for SMA in addition to CF. However, considering the technological advances, ACMG affirmed that "whereas in prior years, carrier screening was a scarce resource reserved only for those with the highest risk, a more attainable price point now allows for the opportunity to reach every patient." It caused a change of view for the inclusion of a condition in general population screening, as published last year. In details, ACMG introduces an interesting "overlapping tiered" approach, which identifies four level of screening, where each level includes the previous one. The first tier includes CF and SMA for all and then other conditions to be evaluated according to specific risk (risk-based screening). The second tier also includes those conditions whose carrier

frequency is equal to or greater than 1:100. The third tier additionally includes the conditions with carrier frequency equal to or greater than 1:200 and a group of X-linked diseases listed, with a derived disease prevalence of 1/40,000. Finally, the fourth tier includes rarer conditions (with carrier frequency less than 1:200), leaving the choice to the individual laboratory offering the screening.

Furthermore, ACMG explains the recommendations to use of this approach:

- All pregnant patients and those planning a pregnancy should be offered tier 3 carrier screening for the autosomal recessive and X-linked conditions listed. Reproductive partners of pregnant patients and those planning a pregnancy may be offered tier 3 carrier screening for autosomal recessive conditions listed when carrier screening is performed simultaneously with their partner.
- Tier 4 screening should be considered when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when a family or personal medical history warrants.
- Tier 1 and/or tier 2 screening is not recommended because these do not provide an equitable evaluation of all racial/ethnic groups.
- Tier 4 panels are not recommended as routine offering.

6. Reporting of the results

In accordance with the joint statement of the ACMG, ACOG, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal–Fetal Medicine [8], SIGU recommends that the laboratory carrying out the analysis should report only genes and variants with clear pathogenicity and provide information on the associated clinical condition. Specifically, only "pathogenic" and "likely pathogenic" variants (class 5 and 4) should be reported, while those of uncertain significance (class 3) should not. Notably, the interpretation of the variants is continuously evolving; therefore, it could be necessary to re-evaluate and re-classify them accordingly. Among scientific societies, the ACOG gives no guidance, RANZCOG and ACMG agree that only "pathogenic" and "likely pathogenic" variants should be reported in the report. Additionally, ACMG considers the possibility of reporting a variant of uncertain significance (VUS) in the partner of a known carrier. Pre-conception counseling session ideally addresses return of results when a VUS is identified.

Moreover, on the basis of the analytical validity and known epidemiological data for all conditions included, SIGU considers appropriate to report residual risks (RRs)—defined as the likelihood that the individual may be carrier even after a negative test result. The RR can be calculated as the product of the carrier frequency in the reference population X (1- detection rate). Consequentially, the definition of reproductive risk should even consider whether both partners have been analyzed or not. However, it is recommended to provide the recipients of the CS with a clear explanation about imperfect estimation/approximation of RR. Indeed, the RR is influenced by multiple variable factors and, therefore, may not be always accurate, especially for rarer conditions. These issues are related to genomic regions not fully characterized, ethnic groups with specific allelic frequencies, inaccurate or mixed declared ethnic origin, technical limitations, type of analysis, challenging interpretation of the variants, and test sensitivity. Specifically, ACMG and ACOG argue it is impractical to generate an accurate residual risk when screening is performed on a large number of conditions, while RANZCOG suggests that all individuals/couples should be informed about the residual chance of the couple having a child with one of the conditions screened for.

7. Cost-efficiency evaluation

Cost-effectiveness evaluates both costs (e.g., cost of CS and the downstream costs of genetic counseling, partner testing, prenatal diagnosis) and clinical benefits (e.g., avoiding affected births) of medical interventions. It is described by a single number (incremental cost-effectiveness ratio (ICER)) that summarizes the cost (e.g., dollars) per unit of health benefit outcome (e.g., life-years gained). This framework allows for comparisons among medical interventions that maximize patient health and, at the same time, optimally allocate health resources, often limited in social welfare.

In the literature background, only two papers examined the cost-effectiveness analysis of CS panels compared to the US benchmark value of $50,000 as cost per life-year gained.

Azimi et al. develop a decision tree model, for comparing NGS-based carrier screening for 14 conditions, recommended by medical society guidelines, versus no screening [43]. Carrier frequency of disorders, patient ethnicity, mutation detection rates, healthcare processes, patient behaviors, costs, and health utilities, among others, are used as parameters in this analysis. The study shows that CS is effective with a cost of $30,000 per life-year gained as compared with no screening.

Beauchamp et al. (2019) analyze the clinical impact and cost effectiveness of a CS panel for 176 conditions using a decision tree model comparing it versus minimal CS screening (23 CF variants + SMA) [44]. The authors estimate that approximately 1:300 pregnancies will be affected by one out of 176 screened conditions, which individually incur $1,100,000 in lifetime costs. According to this study, an increased CS is cost-saving because after subtracting the price of minimal screening, the cost per life-year is negative.

Moreover, it remains cost-effective (< $50,000 per life-year gained), at prices up to $2500 because the net averted costs are greater than the price.

In the Italian context, the SIGU working group underlines that the design of a cost-effectiveness study of CS panels would need a huge amount of data, some of which are very difficult to obtain, for example: the precise content of the panel employed, with its detection rate and cost; the possible reproductive options and their corresponding costs for the at-risk couples (probably divergent from those reported in the US models); the affected individuals for each selected disease; the healthcare costs per year of life; and thus the cost-savings due to the avoided affected births. Beside these issues, some insights from a cost-effectiveness analysis on CS implementation in the National Healthcare System (NHS) were recently provided as preliminary study for the Italian setting [38]. This decision model compared two CS panels—a screening for 21 common conditions in the Mediterranean population and a minimal one only testing CF, SMA, beta-thalassemia, phenylketonuria, and FXS—versus no screening. Both tested CS panels would be dominant versus no screening and cost-effective if reimbursed by NHS.

Generally, it is considered reasonable to widen the included conditions to less frequent ones when this will not significantly increase the costs. On the other hand, some conditions with a high frequency may not be included in the CS panel because they are investigated only with ancillary testing causing relevant increase in testing cost.

Unfortunately, there is not enough data to evaluate the overall cost-effectiveness, so more research on the topic is required. However, all scientific societies agree that carrier screening will be considered cost-effective both for the patient and for the healthcare system because testing costs will be reduced and expensive treatments for genetic disorders will become available.

8. Ethical reflections

CS programs should consider a number of ethical issues both for general population [45] and for "selective" contexts such as assisted reproduction and donor conception [5, 46]. Overall, the ethical debate is aimed at providing direction on the fact that the potential benefits of such screening clearly outweigh the potential harms and disadvantages. The discussion ranges from the scope of carrier screening (i.e., autonomy or prevention) to parental and professional responsibilities as well as the concepts of proportionality and justice. However, it is noted that ethical objections have not a directive effect and should be always applied in accordance with the relevant medico-legal norms in each country's jurisdiction.

The SIGU working group extensively discussed several ethical topics, including (i) justice, avoiding stigmatization and social discrimination and preserving privacy and economic resources of the healthcare system; (ii) autonomy, promoting decision-making and self-determination while considering the risk of medicalization and routinization; and (iii) consequences on personal (i.e., parental responsibility, stressful experience) and public (i.e., welfare and public health costs) spheres. Overall, the working group fully endorses the most recent ESHRE position on the ethical boundaries of CS [5].

Among other scientific societies, ACOG for example gives no guidance, whereas RANZCOG and ACMG agree that CS programs should promote equity and inclusion.

Remarkably, CS programs should be more inclusive of diverse populations (i.e., ethnic neutral) and socio-economic classes (i.e., no financial barrier).

9. Informed consent model

As the basis of decision-making and self-determination, there is the process of informed consent, which broadly explains the indications and implications of CS testing and describes the types of conditions being screened as well as the limitations. However, it is to be noted that it is challenging to illustrate hundreds of different conditions, thus providing detailed information for each screened condition may be impractical. Moreover, screening panels may change over time, and there may be differences between laboratories in the conditions screened.

SIGU claims that all individuals/couples having carrier screening should provide written informed consent model that should be discussing:

(i) Carrier screening of any nature is voluntary, and it is reasonable to accept or decline.
(ii) Screening will not identify carrier status for all disease-causing genes and all mutations in the tested genes and therefore that there is a residual chance of the couple having a child with a genetic disease, including one of the conditions screened for.

All this information should be carefully discussed during pre-test counseling, before signing the written informed consent form and educating patients may be done verbally or by using other informational tools.

All four societies give precise guidance about the points that the informed consent should contain. In brief, ACMG and ACOG, along with other professional organizations, published a joint statement [8] emphasizing that seven components of consent should be included (Table 1). RANZCOG agrees on the residual risk and the possibility to find out that the patient has a genetic condition that could affect his personal health. Moreover, it underlines that if the members of the couple have children with a different partner, they

Table 2 Capsule summary of SIGU recommendations for carrier screening

Objective	• To make reproductive choices easier for at-risk prospective parents, proof of clinical utility
Recipients	• All couples planning a pregnancy, including gamete donors, with particular awareness for consanguineous couples
Timing	• Best at pre-conceptional stage or reporting by the no 12th gestational week if CS is performed during pregnancy
Technical-scientific issues	• The test should be performed by NGS along with more appropriate separated techniques. Requirements for analytical and clinical validity must be met • The inclusion criteria for selecting analyzed conditions should be a clear gene-disease association, negative effects on the quality and/or duration of life, be the cause of physical/cognitive deficits, necessitate medical interventions, present with an early onset, and be a condition diagnosed in PGT or PND
Reporting	• Only class 4 or likely pathogenetic and class 5 or pathogenetic variants should be reported • Residual risk should be provided and/or discussed
Socio-economic issues	• The test is supposed to be cost-effective • The test should promote justice and autonomy and preserve parenthood and the healthcare system

need rescreening to define the reproductive risk for that new couple.

In addition, SIGU offers an informed consent (IC) template form that is ready to use by laboratories offering CS screening and a specific information notice which can be used for educational purposes.

Key message on genetic counseling

Genetic counseling refers to guidance relating to genetic disorders that a specialized healthcare professional provides to an individual or family. Based on clinical opinion and expertise, the provision of genetic counseling in the context of CS programs is claimed by the entire scientific community.

Indeed, while carrier screening is linked to the concept of self-determination, defined as the ability to make decisions for yourself to enhance reproductive autonomy, there is an unquestionable risk of incomplete and insufficient comprehension of the analytical details and limitations of the test, offering CS testing solely. Thus, genetic counselors represent a crucial part of an appropriate reproductive management, providing prospective parents with pathways of pre- and post-test counseling about CS testing.

A detailed pre-test counseling should be carried out explaining benefits and limitations of the test and reporting information about its sensitivity, specificity, and residual risk. Regarding residual risk, it is particularly important to underline that the test does not guarantee the absence of genetic diseases in the offspring but drastically reduces the risk according to the test's limitations.

Afterwards, once the test's results are available, the counseling should support the couple during post-test decision-making. Especially in case of positive CS results, either in one or both members of the couple, post-test counseling is fundamental to interpret the data, assess recurrence risks and clinical features, and evaluate, case by case, possible options for further analysis on the partners and cascade testing on the family members.

Conclusion: SIGU summary and future challenges

In light of emerging scientific evidence and technological advancements, SIGU has expressed for the first time a favorable opinion on the feasibility of genetic testing for the risk assessment of recessive disorders.

The latest recommendations from SIGU were divided into nine discussion sections, a concise summary of which is shown in Table 2.

To extend the discussion, Italy's position on CS was compared to that of other countries. Three overseas scientific organizations were chosen as references: RANZCOG for Oceania and ACOG and ACGM representing America. The level of agreement among the four societies was then evaluated. Each of the nine sections was assigned a score ranging from one to five, with one representing the least amount of agreement and five representing the greatest amount of agreement. Overall, all societies demonstrated a high level of consensus (score of 4 and 5). There was no section that received a score of 1 or 2. With a final score of agreement of 3 out of 5, the societies had a slight disagreement only on which conditions should be screened ("Which and how many conditions?" section) and what information should be given to patients ("Informed consent model" section).

Despite minor differences, the driving principles remained the same. In the "Which and how many conditions?" section, all societies advise against an arbitrary increase in the number of analyzed conditions. Concerning the "Informed consent model" section, societies concurred that informed consents should be designed so that patients can be educated about the test and the conditions in order to improve their ability to make informed decisions.

Finally, there are a few pressing issues that require attention. As thoroughly discussed in the test, when providing genetic testing, it is fundamental to provide genetic counseling too. A healthcare professional is required to explain the test and its clinical importance to couples during a pre-test session. Similarly, counseling should be

provided in a more detailed discussion with the couples about both positive and negative CS test results, during the unavoidable post-test session. Due to the lack of clinical geneticists in Italy, as well as in many other countries, it is clear that providing both pre- and post-test counseling can be problematic. A solution could be the introduction of a new healthcare professional, the genetic counselor, a role that already exists in countries such as the UK and the USA.

In addition, the NHS currently does not perform carrier screenings in Italy. Private companies, on the other hand, have performed the majority of these tests over the years and gained enough knowledge about technological advances in sequencing, interpretation, and variant reporting to assist the NHS through specific agreements. CS is set to become a valid option in the very next future both in terms of cost savings and in limiting individual and family suffering. Subsequently, the public health decision-makers should consider the possibility to offer/reimburse CS to the general population within the Italian tax-based NHS, at least for the more frequent recessive diseases with unquestionable clinical utility.

Ideally, this work, along with its key points for correct CS performance, will be useful guidance for healthcare personnel and will serve as an educational tool efficacious in explaining the implications and limitations of the test to prospective parents.

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Declarations

Conflict of interest A.C. is full time employee at Juno Genetics, providing reproductive genetic services. S.C. is full-time employee at Igenomix Italia, providing reproductive genetic services. L.P., I.G., P.C., F.L., S.B., E.G. and D.Z. have no conflict of interest to disclose.

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